Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Insect Science

Plant toxins and parasitoid trophic ecology

Paul J Ode

Parasitoids (parasitic wasps) are ubiquitous components of nearly all communities containing plant–insect herbivore associations. Plant toxin defenses against herbivores may also affect higher trophic levels by directly (e.g., plant toxins encountered in host hemolymph) or indirectly (e.g., plant toxins reduce host size/quality or alter the host's immunity against parasitoids). Yet, whether parasitoids structure plant–herbivore interactions remains relatively understudied. Nevertheless, recent meta-analyses and empirical work emphasize the importance of parasitoids in structuring interactions among lower trophic levels. Two promising areas of research are particularly ripe for future exploration: a) the potential for microbes to alter the interactions among plants, insect herbivores, and parasitoids, and b) the effects of climate change on phenological (mis)matches among trophic levels.

Address
Department of Bioagricultural Sciences and Pest Management and the Graduate Degree Program in Ecology, Colorado State University, Fort Collins, CO 80523-1177, United States

Corresponding author: Ode, Paul J (paul.ode@colostate.edu)

Current Opinion in Insect Science 2019, **32**:118–123

This review comes from a themed issue on **Ecology**

Edited by **Michael Singer**, **Katerina Sam** and **Genoveva Rodríguez-Castañeda**

For a complete overview see the Issue and the Editorial

Available online 22nd January 2019

https://doi.org/10.1016/j.cois.2019.01.007

Introduction

The extreme biodiversity of plants and their insect herbivores are widely thought to have arisen from reciprocal selection between plant investment in chemical defenses and the various means employed by herbivores to detoxify, excrete, or even sequester the plant toxins that they encounter during feeding [1–4]. Much has been learned about the diversity of plant defense chemicals [5], the mechanisms underlying toxicity to insect herbivores, and the ability of herbivores to cope with plant defenses [e.g., Refs. 5,6]. Furthermore, a growing number of studies have shown that higher trophic levels are influenced by the interactions between plants and herbivores [reviewed in Refs. 7,8]. Nevertheless, whether other community members such as parasitoids and microbes influence the outcome of plant–herbivore interactions remains understudied [9,10]. A recent meta-analysis compared the relative contributions of bottom-up (e.g., plant anti-herbivore traits) versus top-down (predators and parasitoids) effects on herbivore fitness correlates (e.g., abundance, survivorship) [11•]. Interestingly, and contrary to widely held presumptions about the predominant strength of bottom-up forces, the magnitude of effect of top-down forces was found to be generally larger than that of bottom-up forces across several different herbivore feeding guilds (e.g., chewing, sucking, and gall-forming herbivores). The clear lesson from this analysis is that plant–herbivore interactions should not be studied in isolation.

Prominent among higher trophic level members are parasitoids, most of which are parasitic wasps and flies, whose offspring are parasitic as immatures but free living as adults. Virtually all insect species are attacked by one or more parasitoid species. Indeed, most parasitoids themselves are attacked by higher trophic level parasitoids (so-called 'hyperparasitoids'), often further complicating the relationships among lower trophic levels. Parasitoids, especially endoparasitoids whose larvae develop inside their hosts, of insect herbivores almost always have to cope with the effects of plant toxins [12]. While the role of parasitoids and predators in reducing herbivore pest populations on agricultural crops is broadly appreciated, their role in regulating herbivore populations and enhancing plant fitness in natural systems is far less studied. Furthermore, tritrophic interactions between plants, insect herbivores, and parasitoids are likely mediated by microbes including plant pathogens or symbiotic polydnaviruses harbored by some parasitoids in the hymenopteran superfamily Ichneumonoidea [13•,14•]. Indirect interactions between parasitoids and microbes may involve alterations in the relative expression of jasmonic acid and salicylic acid (JA- and SA-) based defense pathways, sometimes benefiting parasitoids and sometimes not [15•].

In this review, I consider recent studies that examine how plant toxins affect parasitoid fitness and briefly examine the evidence that parasitoids may influence the expression of plant defense toxins. I largely exclude discussion of inducible plant volatiles involved in indirect defense as this has been well-reviewed elsewhere [e.g., Refs. 16,17]. I then discuss some intriguing studies of how plant–herbivore–parasitoid relationships are modified by their interactions with microbes. Finally, I consider how climate change (esp. studies using latitudinal and elevational gradients as proxies) may alter the community

ecology of plants, insect herbivores, and their natural enemies.

Plant toxin effects on parasitoids

Plant toxins may affect parasitoid fitness in at least one of three ways [12]. First, parasitoids may directly encounter unmetabolized plant toxins or their toxic metabolites in the hemolymph of their hosts. This includes instances where herbivorous hosts sequester plant toxins as a defense against potential attack by predators and parasitoids [10,18,19]. Indeed, a handful of studies have shown that some parasitized herbivores engage in 'self-medication' whereby they prefer to oviposit and feed on more toxic diets to rid themselves of parasites [20–23] even though feeding on toxic diets is costly in terms of reduced herbivore fitness. Second, ingestion of plant defense toxins by the herbivore may result in reduced body size or some other aspect of host quality that in turn negatively affects parasitoid survivorship, body size, and/or brood size. In these cases, parasitoids may not directly encounter plant toxins or their metabolites [7]. Finally, plant defense chemistry may alter the host herbivore's ability to mount a successful immune response against parasitoid eggs and/or larvae. Where studied, herbivores that feed on plants with higher concentrations and diversity of plant toxins appear to be immuno-compromised and suffer increased rates of mortality via parasitism [24,25•]. For instance, when *Pieris rapae* larvae feed on plants containing higher levels of toxic glucosinolates, their ability to encapsulate eggs of the parasitoid *Cotesia glomerata* is reduced [26]. The suggestion from these studies is that plant toxins may increase parasitoid survivorship, although this has yet to be clearly demonstrated.

The degree to which an herbivore successfully metabolizes plant defensive toxins depends in large part on where the insect falls on the specialist-generalist spectrum. More specialized insect herbivores generally possess very efficient detoxification enzymes (e.g., cytochrome p450s, UDP-glycosyltransferases) that show a high degree of specificity towards particular plant toxins [6,27]. Such herbivores are expected to be far less likely to pass plant toxins from their gut into their hemolymph, where they would be encountered by endoparasitoid larvae, because they either metabolize plant toxins into relatively non-toxic byproducts and/or efficiently excrete these toxins in their frass. Obvious exceptions to this, of course, are specialists that sequester plant toxins as defenses against their own natural enemies [18,28]. Herbivores with broader diets typically possess detoxification enzymes that are broader in their substrate activity, but less efficient in their activity against specific toxins [e.g., Ref. 29]. Generalist herbivores are expected to pass greater amounts of plant toxins into their hemolymph than non-sequestering specialist herbivores [28]. Few studies have explicitly examined the effect of herbivore dietary specialization and toxin accumulation within the hemolymph on parasitoids. In one such study, the generalist cabbage looper *Trichoplusia ni* accumulated far higher concentrations of xanthotoxin in its hemolymph than did the specialist parsnip webworm *Depressaria radiella* (=*Depressaria pastinacella*), even though both were fed identical concentrations of this toxin in an artificial diet. In turn, survivorship and brood sizes of the parasitoid *Copidosoma floridanum* (which attacks *T. ni*) were significantly reduced whereas survivorship and brood sizes of *Copidosoma sosares* (the parasitoid of *D. radiella*) were unaffected by similar concentrations of xanthotoxin in its host's diet [30]. While this fits the paradigm outlined above, it is important to recognize that the putative differences between specialist and generalist herbivore could well be confounded with the fact that these two herbivores are from two different lepidopteran families. Replicated comparisons with more closely related specialist and generalist hosts and their parasitoids would certainly strengthen these conclusions.

Do parasitoids influence expression plant chemical defenses?

While many studies have demonstrated the largely negative effects of plant toxins on parasitoids, evidence that parasitoids exert selection on plant investment in defensive chemistry is scant. Several studies have provided evidence that plant fitness can be increased in the presence of parasitoids [reviewed in Ref. 7]. Furthermore, the many successful insect biological control programs suggest that parasitoids can have a positive impact on plant reproductive output [31]. Investment in chemical defenses represents a significant cost for plants [e.g., Refs. 32–35]. Taken together, the presence of parasitoids should relax herbivore selection for investment in chemical defense, particularly if they reduce herbivore damage. Yet, evidence for this relationship is largely lacking. One possible explanation for this may lie in the rather diffuse relationship between most insect herbivores and their host plants. Whereas the majority of parasitoids show a remarkable degree of host specificity [e.g., Ref. 36], the same cannot be said for herbivore plant relationships for the most part [10].

Nevertheless, a handful of studies have shown that parasitoids can influence the induction of plant chemical defenses. In one study, cabbage plants (*Brassica oleracea*) attacked by *Pieris brassicae* (Lepidoptera: Pieridae) caterpillars parasitized by *C. glomerata* differed in their headspace volatile profiles from plants attacked by unparasitized *P. brassicae* [37]. Presumably, foraging adult *C. glomerata* used these differences in volatiles to identify and avoid superparasitizing previously parasitized hosts. Remarkably, another study on *B. oleracea* involving three parasitoids of two herbivores (*P. brassicae* and *P. rapae*) showed that parasitoid species identity, not herbivore identity, differentially induced expression of several genes involved in the jasmonic acid (JA) defense pathway

(e.g., *BoLOX*, *BoMYC*, *BoVSP*) as well as *BoPIN*, which codes for a protease inhibitor that inhibits herbivore protein digestive enzymes [38]. Finally, wild cabbage (*B. oleracea*) populations produced 1.5 times the levels of indole glucosinolates (glucobrassicin and neoglucobrassicin) when attacked by *T. ni* larvae parasitized by *C. floridanum* compared to indole glucosinolate levels induced by unparasitized *T. ni* [39•]. The likely explanation for this is the fact that *T. ni* parasitized by *C. floridanum* consume up to 50% more plant tissue compared to unparasitized *T. ni*.

Microbes and tritrophic interactions

It is increasingly recognized that microbial associates of herbivores and/or their parasitoids interact with the expression of plant defense chemistry, thereby altering the functioning trophic relationships [15•,40]. One of the earliest studies to document the role of symbiotic bacteria and chewing insect herbivores involved the three bacterial genera (*Stenotrophomonas*, *Pseudomonas*, and *Enterobacter*), Colorado potato beetle (*Leptinotarsa decemlineata*), and tomato (*Solanum lycopersicum*) [41]. Beetle larvae harboring these bacterial symbionts in their oral secretions were shown to induce salicylic acid (SA)-signaling pathways (which result in defenses against microbial pathogens), which in turn suppresses expression of jasmonic acid (JA)-based defenses, which are active against chewing herbivores. Subsequently, an increasing number of studies have implicated microbial associates of herbivores and, in some cases, even of parasitoids in the manipulation of crosstalk between SA-signaling and JA-signaling pathways to the advantage of herbivores (and sometimes parasitoids) [13•,15•,42]. In some cases, parasitoids are more attracted to hosts feeding on plants infected by plant viral [43] or bacterial [44] pathogens, possibly cueing on volatiles enhanced by plant pathogens. A handful of studies have shown that microbial associates of herbivores have been implicated in the detoxification of plant chemical defenses [reviewed in Ref. 15•]. Explicit links to the third trophic level have yet to be made, but parasitoids likely benefit from such relationships between herbivores and microbes.

Polydnaviruses are obligately symbiotic viruses associated with many parasitoids within the hymenopteran superfamily Ichneumonoidea (Braconidae and Ichneumonidae). Polydnaviruses are widely appreciated for their roles in suppression of host herbivore immune responses to parasitoids [45,46]. However, polydnaviruses have recently been implicated in the manipulation of plant anti-herbivore defenses. The polydnavirus of the braconid parasitoid *Microplitis croceipes* suppresses the production of glucose oxidase in the saliva of its host, *Helicoverpa zea* (Noctuidae) [13•]. Glucose oxidase is an important plant-defense elicitor; suppression of this elicitor and, subsequently expression of plant anti-herbivore defenses, allows *H. zea* to grow more quickly to the benefit of the parasitoid [13•]. Yet, despite their advantages to parasitoids, polydnaviruses may be detrimental in some cases. The polydnavirus of the braconid parasitoid *C. glomerata* alters the salivary elicitors of the caterpillar host *P. brassicae* [14•]. This, in turn, induces changes in herbivore-induced plant volatiles (HIPVs) emitted by the host plant, wild cabbage *B. oleracea* [14•]. Finally, *Lysibia nana*, a hyperparasitoid of *C. glomerata*, uses the altered HIPVs released by the cabbage plant to locate its host [14•]. Given the estimated 65 000 species of ichneumonoid parasitoids [47], the role that polydnaviruses play in the expression of plant chemical defenses and the resulting herbivore-parasitoid relationships are likely very widespread.

Climate change and changing trophic interactions

The likelihood and intensity of herbivory are often presumed to be higher at lower latitudes and lower elevations [48,49•]; correspondingly, plant investment in defenses should be higher at lower latitudes and elevations [e.g., latitudinal herbivory-defense hypothesis, LHDH; 50]. Some within-genus comparative studies have broadly supported this pattern. For instance, milkweed species (*Asclepias* spp.) in the tropics generally contain higher levels of both constitutive and inducible cardenolides than species at higher latitudes [51]. Similarly, tannin concentrations in oaks (*Quercus* spp.) were greater at lower latitudes [52]. However, other studies have found either no relationship or even greater levels of defenses at higher latitudes [53–56]. For instance, a recent study of latitudinal variation in phenolic production across 80 species of *Oenothera* (Onagraceae) showed that defense investment was greater at higher altitudes and lower temperatures [48], presumably due to higher herbivore pressure in this genus in colder climates. Similarly, recent syntheses of the relationships between plant defenses, herbivory, and elevation are not as straightforward as originally thought; rather these relationships are driven by an array of abiotic and biotic conditions that vary across elevation [49•,57•,58]. Reciprocal transplant studies involving multiple trophic levels can be invaluable in teasing apart the roles of biotic and abiotic factors underlying local adaptation that vary across latitude [e.g., Ref. 59] and elevation [e.g., Ref. 60•]. It is important to note that the elevation/latitude correlations with levels of plant defense investment and herbivory have rarely been extended to higher trophic levels [e.g., Refs. 61,62]. Nevertheless, we can make reasonable speculations about the effects on parasitoids based on the relationships outlined above. For instance, in systems where the LHDH appears to hold, should herbivores and parasitoids expand their ranges poleward or to higher elevations response to warming climates, they may encounter plants that invest little in defenses. The net effect of herbivore and parasitoid range expansion will depend on the system-specific effects of

plant toxins on herbivore–parasitoid interactions described above.

Studies across elevation gradients have long been used as proxies to understand the effects of climate change on trophic interactions across latitudinal gradients [e.g., Refs. 63,64]. The phenologies of ectothermic organisms such as plants and insects are highly sensitive to changes in temperature [65] that occur across elevation gradients. If plants, insect herbivores, and their parasitoids differentially respond to changes in temperature, phenological mismatches may arise that effectively break trophic links (or matches can be formed that establish novel trophic relationships) [66–70]. In particular, plants that span broad elevational gradients often escape their higher trophic levels (possibly because of phenological mismatches) at higher elevations [e.g., Ref. 61]. Given the potentially strong top-down effects of parasitoids on plant–herbivore relationships [e.g., Ref. 11•], changes in trophic structure and community ecology resulting from phenological mismatches/matches are expected to alter the effects of plant chemistry on parasitoids as well as the effects parasitoids on plant investment in chemical defenses and their interactions with herbivores.

Conclusions and future directions

Great strides have been made in our understanding of the complex interactions between plants (esp. plant defense traits), insect herbivores, and microbes [15•,40]. Similarly, several recent syntheses have addressed how both abiotic and biotic factors can potentially influence plant defense and plant–herbivore interactions along elevational gradients [e.g., Refs. 49•,57•,58]. Several of these studies have included natural enemies, including parasitoids. A growing number of studies have shown that parasitoids are clearly affected by plant defense traits—either via indirect HIPVs that are used by parasitoids to locate potential hosts or via plant defense toxins that are directly encountered by the parasitoids in their hosts or that degrade host quality for the parasitoid. As pointed out by others [e.g., Ref. 49•], most of these studies have been correlational with little understanding of the underlying mechanisms responsible for these patterns. Manipulative studies such as reciprocal transplant and common garden experiments [e.g., Refs. 59,60•] can help tease apart the relative contributions of various biotic and abiotic factors in driving relationships between plant defense, insect herbivores, and their parasitoids. Such approaches are critical if we are to fully understand the effects of climate change on biodiversity. Nevertheless, despite their ubiquity, the role of parasitoids in structuring communities is still poorly understood. Whether parasitoids and other natural enemies are passive participants in multitrophic interactions with little influence on the outcome of lower trophic interactions or if they play a central role in determining the outcome of plant–herbivore and even plant–microbe interactions remains to be resolved. Yet, despite evidence for the strong top-down effects of parasitoids [11•], studies clearly integrating the potential effects of herbivore natural enemies in consideration of plant–herbivore and plant–microbe interactions remain few.

Conflict of interest statement

Nothing declared.

Acknowledgements

I thank Katerina Sam for the invitation to contribute this manuscript. PJO was supported by United States Department of Agriculture NIFA AFRI grant 2014-67013-.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest

1. Erlhich PR, Raven PH: **Butterflies and plants: a study in coevolution**. *Evolution* 1964, **18**:586-608.
2. Mitter C, Farrell B, Wiegmann B: **The phylogenetic study of adaptive zones: has phytophagy promoted insect diversification?** *Am Nat* 1988, **132**:107-128.
3. Richards LA, Dyer LA, Forister ML, Smilanich AM, Dodson CD, Leonard MD, Jeffrey CS: **Phytochemical diversity drives plant-insect community diversity**. *Proc Natl Acad Sci U S A* 2015, **112**:10973-10978.
4. Speed MP, Fenton A, Jones MG, Ruxton GD, Brockhurst MA: **Coevolution can explain defensive secondary metabolite diversity in plants**. *New Phytol* 2015, **208**:1251-1263.
5. Moore BD, Andrew RL, Külheim C, Foley WJ: **Explaining intraspecific diversity in plant secondary metabolites in an ecological context**. *New Phytol* 2014, **201**:733-750.
6. Heidel-Fischer HM, Vogel H: **Molecular mechanisms of insect adaptation to plant secondary compounds**. *Curr Opin Insect Sci* 2015, **8**:8-14.
7. Ode PJ: **Plant chemistry and natural enemy fitness: effects on herbivore and natural enemy interactions**. *Annu Rev Entomol* 2006, **51**:163-185.
8. Ode PJ: **Plant defences and parasitoid chemical ecology**. In *Chemical Ecology of Insect Parasitoids.* Edited by Wajnberg Eaue., Colazza S. Wiley-Blackwell; 2013:11-36.
9. Singer MS, Stireman JO: **The tri-trophic niche concept and adaptive radiation of phytophagous insects**. *Ecol Lett* 2005, **8**:1247-1255.
10. Futuyma DJ, Agrawal AA: **Macroevolution and the biological diversity of plants and herbivores**. *Proc Natl Acad Sci U S A* 2009, **106**:18054-18061.
11. • Vidal MC, Murphy SM: **Bottom-up vs. top-down effects on terrestrial insect herbivores: a meta-analysis**. *Ecol Lett* 2018, **21**:138-150.

This important meta-analysis compared the relative strength of top-down versus bottom-up control of herbivore populations from 75 publications. Interestingly, top-down effects were significantly stronger than bottom-up effects across several types of insect herbivore guilds including chewing, piercing-sucking, and gall-forming insects in both managed and natural environments.

12. Kaplan I, Carrillo J, Garvey M, Ode PJ: **Indirect plant-parasitoid interactions mediated by changes in herbivore physiology**. *Curr Opin Insect Sci* 2016, **14**:112-119.
13. • Tan C-W, Peiffer M, Hoover K, Rosa C, Acevedo FE, Felton GW: **Symbiotic polydnavirus of a parasite manipulates caterpillar and plant immunity**. *Proc Natl Acad Sci U S A* 2018, **115**:5199-5204.

A fascinating study that demonstrates the role of polydnaviruses in suppressing plant anti-herbivore responses. Polydnaviruses, obligate

symbionts of braconid parasitoids usually associated with compromising host immune responses, are shown here to suppress glucose oxidase, an important plant-defense elicitor found in the saliva of the host herbivore. Ultimately, the benefit of the polydnavirus to the parasitoid is two-fold: a) suppression of the host's immune response, and b) suppresses elicitation of plant defenses allowing the host to grow more quickly to the benefit of the parasitoid.

14. • Zhu F, Cusumano A, Bloem J, Weldegergis BT, Villela A, Fatouros NE, van Loon JJA, Dicke M, Harvey JA, Vogel H, Poelman EH: **Symbiotic polydnavirus and venom reveal parasitoid to its hyperparasitoids**. *Proc Natl Acad Sci U S A* 2018, **115**:5205-5210.

Another intriguing study demonstrating a novel role of symbiotic polydnaviruses in braconid parasitoids. Unlike Tan*et al.* [13], polydnaviruses in this study are shown to have a potentially negative effect on the their *Cotesia* parasitoids. The authors show that the polydnavirus is implicated in altering the activity of the host caterpillar's salivary elicitors. This changes the volatile profile of damaged plants, which in turn attracts hyperparasitoids that attack the *Cotesia* parasitoids.

15. • Shikano I, Rosa C, Tan C-W, Felton GW: **Tritrophic interactions: microbe-mediated plant effects on insect herbivores**. *Annu Rev Phytopath* 2017, **55**:313-331.

An excellent overview of the often-surprising roles that microbes (both plant-associated and insect-associated) can play in altering the tritrophic interactions among plants, insect herbivores, and their natural enemies.

16. Rowen E, Kaplan I: **Eco-evolutionary factors drive induced plant volatiles: a meta-analysis**. *New Phytol* 2016, **210**:284-294.

17. Ameye M, Allmann S, Verwaeren J, Smagghe G, Haesaert G, Schuurink RC, Audenaert K: **Green leaf volatile production by plants: a meta-analysis**. *New Phytol* 2018, **220**:666-683.

18. Nishida R: **Sequestration of defensive substances from plants by Lepidoptera**. *Annu Rev Entomol* 2002, **47**:57-92.

19. Reudler JH, van Nouhuys S: **The roles of foraging environment, host species, and host diet for a generalist pupal parasitoid**. *Entomol Exp Appl* 2018, **166**:251-264.

20. Singer MS, Mace KC, Bernays EA: **Self-medication as adaptive plasticity: increased ingestion of plant toxins by parasitized caterpillars**. *PLoS One* 2009, **4**:e4796.

21. Smilanich AM, Mason PA, Sprung L, Chase TR, Singer MS: **Complex effects of parasitoids on pharmacophagy and diet choice of a polyphagous caterpillar**. *Oecologia* 2011, **165**:995-1005.

22. Milan NF, Kacsoh BZ, Schlenke TA: **Alcohol consumption as self-medication against blood-borne parasites in the fruit fly**. *Curr Biol* 2012, **22**:488-493.

23. Kacsoh BZ, Lynch ZR, Mortimer NT, Schlenke TA: **Fruit flies medicate offspring after seeing parasites**. *Science* 2013, **339**:947-950.

24. Smilanich AM, Dyer LA, Chambers JQ, Bowers MD: **Immunological cost of chemical defence and the evolution of herbivore diet breadth**. *Ecol Lett* 2009, **12**:612-621.

25. • Hansen AC, Glassmire AE, Dyer LA, Smilanich AM: **Patterns in parasitism frequency explained by diet and immunity**. *Ecography* 2017, **40**:803-805.

The authors show that*Eois* spp. caterpillars exhibit suppressed immune responses, as measured by phenoloxidase activity, when reared on *Piper* plants that possess higher concentrations of toxic amides and imides. Using a 19-year field data set, the authors suggest that this pattern explains the increased rates parasitism of *Eois* caterpillars collected from more toxic *Piper* species.

26. Bukovinsky T, Poelman EH, Gols R, Prekatsakis G, Vet LEM, Harvey JA, Dicke M: **Consequences of constitutive and induced variation in plant nutritional quality for immune defence of a herbivore against parasitism**. *Oecologia* 2009, **160**:299-308.

27. Mao W, Rupasinghe S, Zangerl AR, Schuler MA, Berenbaum MR: **Remarkable substrate-specificity of CYP6AB3 in *Depressaria pastinacella*, a highly specialized caterpillar**. *Insect Mol Biol* 2006, **15**:169-179.

28. Ali JG, Agrawal AA: **Specialist versus generalist insect herbivores and plant defense**. *Trends Plant Sci* 2012, **17**:293-302.

29. Li X, Baudry J, Berenbaum MR, Schuler MA: **Structural and functional divergence of insect CYP6B proteins: from specialist to generalist cytochrome P450**. *Proc Natl Acad Sci U S A* 2004, **101**:2939-2944.

30. Lampert EC, Zangerl AR, Berenbaum MR, Ode PJ: **Generalist and specialist host-parasitoid associations respond differently to wild parsnip (*Pastinaca sativa*) defensive chemistry**. *Ecol Entomol* 2011, **36**:52-61.

31. Peterson JA, Ode PJ, Oliveira-Hofman C, Harwood JD: **Integration of plant defense traits with biological control of arthropod pests: challenges and opportunities**. *Front Plant Sci* 2016, **7**:1794 http://dx.doi.org/10.3389/fpls.2016.01794.

32. Berenbaum MR, Zangerl AR: **Costs of inducible defense: protein limitation, growth, and detoxification in parsnip webworms**. *Ecology* 1994, **75**:2311-2317.

33. Zangerl AR, Berenbaum MR: **Cost of chemically defending seeds: furanocoumarins and *Pastinaca sativa***. *Am Nat* 1997, **150**:491-504.

34. Bekaert M, Edger PP, Hudson CM, Pires JC, Conant GC: **Metabolic and evolutionary costs of herbivory defense: systems biology of glucosinolate synthesis**. *New Phytol* 2012, **196**:596-605.

35. Züst T, Rasmann S, Agrawal AA: **Growth-defense tradeoffs for two major anti-herbivore traits of the common milkweed *Asclepias syriaca***. *Oikos* 2015, **124**:1404-1415.

36. Smith MA, Rodriguez JJ, Whitfield JB, Deans AR, Janzen DH, Hallwachs W, Hebert PDN: **Extreme diversity of tropical parasitoid wasps exposed by iterative integration of natural history, DNA barcoding, morphology, and collections**. *Proc Natl Acad Sci U S A* 2008, **105**:12359-12364.

37. Fatouros NE, van Loon JJA, Hordijk KA, Smid HM, Dicke M: **Herbivore-induced plant volatiles mediate in-flight host discrimination by parasitoids**. *J Chem Ecol* 2005, **31**:2033-2047.

38. Poelman EH, Zhen S-J, Zhang Z, Heemskerk NM, Cortesero A-M, Dicke M: **Parasitoid-specific induction of plant responses to parasitized herbivores affects colonization by subsequent herbivores**. *Proc Natl Acad Sci U S A* 2011, **108**:19647-19652.

39. • Ode PJ, Harvey JA, Reichelt M, Gershenzon J, Gols R: **Differential induction of plant chemical defenses by parasitized and unparasitized herbivores: consequences for reciprocal, multitrophic interactions**. *Oikos* 2016, **125**:1398-1407.

The first study to document the differential induction of plant toxins by parasitized caterpillars. Parasitized caterpillars feed more, resulting in increased induction of indole glucosinolate defenses. The implication is that parasitoids can influence the expression of direct plant defenses against herbivores.

40. Tack AJM, Dicke M: **Plant pathogens structure arthropod communities across multiple spatial and temporal scales**. *Funct Ecol* 2013, **27**:633-645.

41. Chung SH, Rosa C, Scully ED, Peiffer M, Tooker JF, Hoover K, Luthe DS, Felton GW: **Herbivore exploits orally secreted bacteria to suppress plant defenses**. *Proc Natl Acad Sci U S A* 2013, **110**:15728-15733.

42. Luna E, van Eck L, Campillo T, Weinroth M, Metcalf J, Botha A-M, Thannhauser TW, Pappin D, Tisserat NA, Lapitan NLV *et al.*: **Bacteria associated with Russian wheat aphid (*Diuraphis noxia*) enhance aphid virulence to wheat**. *Phytobiomes* 2018, **2**:151-164.

43. Mauck KE, Smyers E, De Moraes CM, Mescher MC: **Virus infection influences host plant interactions with non-vector herbivores and predators**. *Funct Ecol* 2015, **29**:662-673.

44. Martini X, Pelz-Stelinski KS, Stelinski LL: **Plant pathogen-induced volatiles attract parasitoids to increase parasitism of an insect vector**. *Front Ecol Evol* 2014, **2**:8 http://dx.doi.org/10.3389/fevo.2014.00008.

45. Strand MR, Burke GR: **Polydnaviruses: nature's genetic engineers**. *Annu Rev Virol* 2014, **1**:333-354.

46. Drezen J-M, Chevignon G, Louis F, Huguet E: **Origin and evolution of symbiotic viruses associated with parasitoid wasps**. *Curr Opin Insect Sci* 2014, **6**:35-43.

47. Rodriguez JJ, Fernández-Triana JL, Smith AM, Janzen DH, Hallwachs W, Erwin TL, Whitfield JB: **Extrapolations from field studies and known faunas converge on dramatically increased estimates of global microgastrine parasitoid species richness (Hymenoptera: Braconidae)**. *Insect Cons Diver* 2013, **6**:530-536.

48. Anstett DN, Ahern JR, Johnson MTJ, Salminen J-P: **Testing for latitudinal gradients in defense at the macroevolutionary scale**. *Evolution* 2018, **72**:2129-2143.

49. • Moreira X, Petry WK, Mooney KA, Rasmann S, Abdala-Roberts L: **Elevational gradients in plant defences and insect herbivory: recent advances in the field and prospects for future research**. *Ecography* 2018, **41**:1485-1496.
A comprehensive review of how trophic interactions change across elevation with insightful recommendations for future research in this area.

50. Schemske DW, Mittelbach GG, Cornell HV, Sobel JM, Roy K: **Is there a latitudinal gradient in the importance of biotic interactions?** *Annu Rev Ecol, Evol, Syst* 2009, **40**:245-269.

51. Rasmann S, Agrawal AA: **Latitudinal patterns in plant defense: evolution of cardenolides, their toxicity and induction following herbivory**. *Ecol Lett* 2011, **14**:476-483.

52. Pearse IS, Hipp AL: **Global patterns of leaf defenses in oak species**. *Evolution* 2012, **66**:2272-2286.

53. Moles AT, Wallis IR, Foley WJ, Warton DI, Stegen JC, Bisigato AJ, Cella-Pizarro L, Clark CJ, Cohen PS, Cornwell WK *et al.*: **Putting plant resistance traits on the map: a test of the idea that plants are better defended at lower latitudes**. *New Phytol* 2011, **191**:777-788.

54. Moles AT, Bonser SP, Poore AGB, Wallis IR, Foley WJ: **Assessing the evidence for latitudinal gradients in plant defence and herbivory**. *Funct Ecol* 2011, **25**:380-388.

55. Johnson MTJ, Rasmann S: **The latitudinal herbivory-defence hypothesis takes a detour on the map**. *New Phytol* 2011, **191**:589-592.

56. Anstett DN, Nunes KA, Baskett C, Kotanen PM: **Sources of controversy surrounding latitudinal patterns in herbivory and defense**. *Trends Ecol Evol* 2016, **31**:789-802.

57. • Defossez E, Pellissier L, Rasmann S: **The unfolding of plant growth form-defence syndromes along elevation gradients**. *Ecol Lett* 2018, **21**:609-618.
This study examines trade-offs between growth form and chemical defense in 15*Cardamine* species across an elevation gradient in response to different abiotic and biotic (herbivory) pressures.

58. Kergunteuil A, Descombes P, Glauser G, Pellissier L, Rasmann S: **Plant physical and chemical defence variation along elevation gradients: a functional trait-based approach**. *Oecologia* 2018, **187**:561-571.

59. Abarca M, Lill JT: **Latitudinal variation in the phenological responses of eastern tent caterpillars and their egg parasitoids**. *Ecol Entomol* 2019, **44**:50-61.

60. • Kergunteuil A, Röder G, Rasmann S: **Environmental gradients and the evolution of tri-trophic interactions**. *Ecol Lett* 2019, **22**:292-301 http://dx.doi.org/10.1111/ele.13190.
This study is an excellent example of how reciprocal transplant studies can be used to examine local adaptation in tri-trophic interactions across elevation gradients.

61. Preszler RW, Boecklen WJ: **The influence of elevation on tri-trophic interactions: opposing gradients of top-down and bottom-up effects on a leaf-mining moth**. *Écoscience* 1996, **3**:75-80.

62. Rasmann S, Pellissier L, Defossez E, Jactel H, Kunstler G: **Climate-driven change in plant-insect interactions along elevation gradients**. *Funct Ecol* 2014, **28**:46-54.

63. Parmesan C: **Ecological and evolutionary responses to recent climate change**. *Annu Rev Ecol Evol Syst* 2006, **37**:637-669.

64. Alexander JM, Diez JM, Levine JM: **Novel competitors shape species' responses to climate change**. *Nature* 2015, **525**:515-518.

65. Thackeray SJ, Henrys PA, Hemming D, Bell JR, Botham MS, Burthe S, Helaouet P, Johns DG, Jones ID, Leech DI *et al.*: **Phenological sensitivity to climate across taxa and trophic levels**. *Nature* 2016, **535**:241-245.

66. van Nouhuys S, Lei G: **Parasitoid-host metapopulation dynamics: the causes and consequences of phenological asynchrony**. *J Anim Ecol* 2004, **73**:526-535.

67. Stireman JO III, Dyer LA, Janzen DH, Singer MS, Lill JT, Marquis RJ, Ricklefs RE, Gentry GL, Hallwachs W, Coley PD *et al.*: **Climatic unpredictability and parasitism of caterpillars: implications of global warming**. *Proc Natl Acad Sci U S A* 2005, **102**:17384-17387.

68. Durant JM, Hjermann DO, Ottersen G, Stenseth NC: **Climate and the match or mismatch between predator requirements and resource availability**. *Clim Res* 2007, **33**:271-283.

69. Schweiger O, Settele J, Kudrna O, Klotz S, Kühn I: **Climate change can cause spatial mismatch of trophically interacting species**. *Ecology* 2008, **89**:3472-3479.

70. Sundqvist MK, Sanders NJ, Wardle DA: **Community and ecosystem responses to elevational gradients: processes, mechanisms, and insights for global change**. *Annu Rev Ecol Evol Syst* 2013, **44**:261-280.